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(54) Title: SELECTIVE LIGANDS FOR THE DELTA OPIOID RECEPTOR

(57) Abstract: Ligands which are selective for the delta opioid receptor. The ligands may be used for treating a variety of disease states.

SELECTIVE LIGANDS FOR THE DELTA OPIOID RECEPTOR

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to ligands which are selective for the delta opioid receptor. The present invention also relates to the use of these ligands for treating a variety of disease states.

Background of the Invention

Since the discovery of the non-peptide δ-opioid receptor selective compounds, BW373U86 (**1**)[1] and SNC-80 (**2**),[2] a great variety of new opioid ligands[3,4] have appeared utilizing the diethylbenzamide substructure to influence δ-selectivity (see Figure 1). This unique δ-address moiety has been incorporated into both classical and non-classical opioid ligands[5] in a search for analgesics possessing a reduced side-effect profile relative to the μ opioid analgesic morphine. Several groups, including our own,[3,6,7] have studied the effect on overall ligand activity produced by transposition of the internal nitrogen atom in compound **1** with the benzylic carbon as represented by compound **3** (see Figure 1). These compounds were found to be δ-receptor selective full agonists with the potency being directly affected by the 3-methyl group as well as its *cis* relative disposition to the 4-diaryl system. Recent reports of antagonist activity in compound **4** by Chang et al.[8] demonstrated that alteration of the placement of the methyl groups in **1**, and consequently, the conformational disposition of the piperazine ring could convert agonists into antagonists.

Relative to the piperazine analogs **1** or **2**, the piperidine compound **3** is more conformationally flexible. The reports of the antagonistic activity of the more structurally rigid **4** suggested that at least part of this effect could result from a decrease in conformational flexibility of **4**, and thus, antagonist activity might be elicited from piperidine compounds similar to **3** if the overall system were made more rigid. To test this hypothesis, the tropane (bridged piperidine) derived compounds **5a-d** were prepared and tested in opioid binding and functional assays. In this communication we report that compounds of this nature demonstrate high degrees of delta selectivity and binding affinity as well as antagonist activity with potency modulated by the N-substituent.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide novel compounds which bind to opioid receptors.

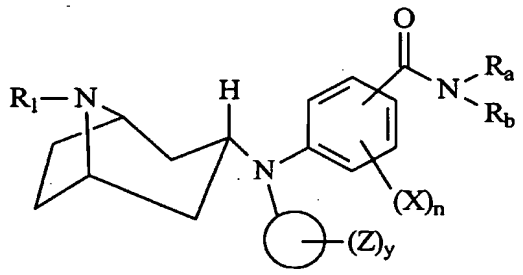
It is another object of the present invention to provide novel compounds which are opioid receptors antagonists that bind with high affinity.

It is another object of the present invention to provide novel opiates that are selective for the delta receptor as compared to the mu and kappa receptors.

It is another object of the present invention to provide methods of making the novel compounds.

It is another object of the present invention to provide methods of treating a variety of disease states with the novel opiate compounds of the present invention.

The objects above may be accomplished with compounds represented by the formula, or pharmaceutically acceptable salts thereof:



where

R_a and R_b are each, independently, hydrogen, an alkyl group or an alkenyl group, or R_a and R_b are bonded together to form an alkyl group;

each X is, independently, an alkyl group;

o is an aryl or heteroaryl group;

each Z is, independently, an alkyl group, -OH, -OR, halogen, $-CF_3$, -CN, $-NH_2$, -NHR, or $-N(R)_2$;

each R is, independently, an alkyl group, an alkenyl group, an aryl group, or an alkaryl group;

n is 0 or an integer from 1 to 4;

y is 0 or an integer from 1 to 5; and

R_1 is an alkyl group, an alkenyl group, or an aralkyl group.

The objects above may also be accomplished with a pharmaceutical composition containing a compound of the present invention and a pharmaceutically acceptable carrier or diluent.

The objects above may also be accomplished with a method of binding opioid receptors, comprising administering an effective amount of the compound of Claim 1 to a mammalian subject in need thereof.

BRIEF DESCRIPTION OF THE FIGURES

A more complete appreciation of the invention and many of the attendant advantages thereof will be readily obtained as the same becomes better understood by reference to the following detailed description when considered in connection with the accompanying drawings, wherein

Figure 1: chemical structure of BW373U86 (**1**), SNC-80 (**2**), compound **3**, and compound 4;

Figure 2: reaction sequence for the preparation of the compounds of the present invention; and

Figure 3: reaction sequence for the preparation of the compounds **5(a-d)** of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

As used throughout this disclosure, the terms "alkyl group" or "alkyl radical" encompass all structural isomers thereof, such as linear, branched and cyclic alkyl groups and moieties. Unless stated otherwise, all alkyl groups described herein may have 1 to 8 carbon atoms, inclusive of all specific values and subranges there between, such as 2, 3, 4, 5, 6, or 7 carbon atoms.

As used herein, the term "alkenyl group" refers to a group which have one or more double bonds, i.e., an alkyl group modified by the presence of at least one double bond. The alkenyl group may have up to three double bonds, more preferably, up to two double bonds, and, most preferably, one double bond. An alkenyl group herein may have 1 to 8 carbon atoms, inclusive of all specific values and subranges there between, such as 2, 3, 4, 5, 6, or 7 carbon atoms. Specific examples of an alkenyl groups include allyl, crotyl (*cis* or *trans*) and prenyl groups. It is to be understood that when an alkenyl group is bonded to a heteroatom, e.g., N or O, there is no double bond between the heteroatom and the carbon atom of the alkenyl group that is bonded to the heteroatom.

As used herein, the term "aryl group" refers to a cyclic aromatic group. The aryl group may contain 6 to 20 carbon atoms. A particularly preferred aryl group is phenyl.

As used herein, the term "heteroaryl group" refers to aryl group in which one or more carbon atoms in the aromatic ring have been replaced with a heteroatom. The heteroaryl group may contain 3 to 20 carbon atoms, inclusive of all specific values and subranges there between. Suitable heteroaryl groups may have one, two, three or four heteroatoms, e.g., nitrogen, oxygen or sulfur. Specific examples of heteroaryl groups include pyridine, pyridazine, pyrimidine, pyrazine, traiazine (e.g., 1,2,3-; 1,2,4-; 1,3,5-), 1,2,4,5-tetrazine, furan, thiophene, oxazole, isothiazole, thiadazole, pyrazole, pyrrole, and imidazole.

As used herein, the term "aralkyl group" refers to an aryl moiety bonded to an alkyl radical. The aryl moiety may have 6 to 20 carbon atoms, inclusive of all specific values and subranges there between. The aralkyl group may have 7 to 25 carbon atoms, inclusive of all specific values and subranges there between. The aryl moiety may contain only carbon and hydrogen atoms. A particularly preferred aryl moiety is phenyl-. An example of an aralkyl group is the benzyl group.

R_a and R_b may each be an alkyl group. Suitable alkyl groups are as defined above. In this embodiment, the preferable alkyl group is ethyl. Alternatively, R_a and R_b may be bonded

to form an alkyl group. In this embodiment, R_a and R_b, together with the nitrogen atom to which they are bonded, form a ring. When R_a and R_b are bonded, the alkyl group has 3 to 7 carbon atoms.

The -C(O)-NR_aR_b moiety may be bonded to the adjacent phenyl ring at the 2-, 3- or 4-position. Preferably, the -C(O)-NR_aR_b moiety is bonded to the adjacent phenyl ring at the 3- or 4-position, more preferably at the 4-position.

Each X, if present, may be an alkyl group. Suitable alkyl groups are as described for R_1 in formula (I) above. The number of X groups, determined by the variable n, may be 0, 1, 2, 3 or 4. Preferably, n is 0.

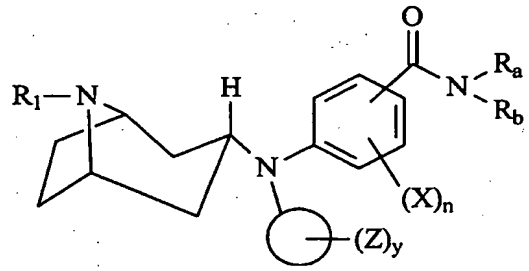
The group ○ is a five- or six-membered aryl or heteroaryl group. Phenyl is the preferred aryl group. Suitable heteroaryl groups may have one, two, three or four heteroatoms, e.g., nitrogen, oxygen or sulfur. Specific examples of heteroaryl groups include pyridine, pyridazine, pyrimidine, pyrazine, triazine (e.g., 1,2,3-; 1,2,4-; 1,3,5-), 1,2,4,5-tetrazine, furan, thiophene, oxazole, isothiazole, thiadazole, pyrazole, pyrrole, and imidazole.

Each Z, if present, is, independently, an alkyl group, -OH, -OR, halogen, $-CF_3$, -CN, $-NH_2$, -NHR, or $-N(R)_2$. The R groups are, independently, an alkyl group, an alkenyl group, an aryl group (such as phenyl) or an aralkyl group group (such as benzyl). A preferred example of Z is a hydroxyl group.

The number of Z groups, determined by the variable y, may be 0, 1, 2, 3, 4, or 5. Preferably, y is 1 or 0. More preferably, y is 1. The Z groups may be present at the 2-, 3- or 4-position of the ring. The 3-position is preferred.

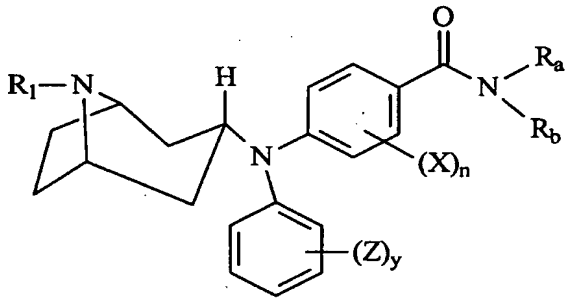
R_1 may be an alkyl group, an alkenyl group, or an aralkyl group. Preferably, these groups have 1 to 8 carbon atoms, more preferably 1 to 5 carbon atoms. The alkenyl group may have up to three double bonds, more preferably, up to two double bonds, and, most preferably, one double bond. One skilled in the art will readily appreciate that the R_1 group is not double-bonded to the adjacent nitrogen atom, i.e., there is no enamine functionality. double bond An alkenyl group is preferred. Preferably, R_1 is an allyl or prenyl group. Most preferably, R_1 is an prenyl group.

In a preferred embodiment, the compounds of the present invention are represented by the formula:



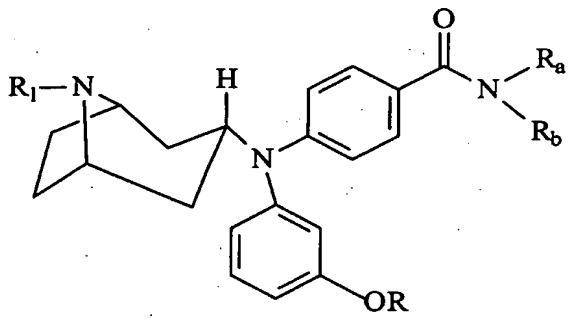
where the -C(O)-NR_aR_b moiety is bonded to the adjacent phenyl ring at the 3- or 4-position, n is 1, and y is 0, 1 or 2

In a more preferable embodiment, the compounds of the present invention are represented by the formula:



where y is 1 and the Z group is bonded to the adjacent phenyl ring at the 3- or 4-position.

In a particularly preferred embodiment, the compounds of the present invention are represented by the formula:



where R is hydrogen or an alkyl group. Examples of alkyl groups are described above. Methyl is the preferred alkyl group.

The compounds of the present invention are opiates which are preferably antagonists that are selective for the delta receptor. The δ/μ selectivity may be at least 2:1, but is preferably higher, e.g., at least 5:1, 10:1, 25:1, 50:1, 100:1 or 200:1. The δ/κ selectivity may be at least 2:1, but is preferably higher, e.g., at least 5:1, 10:1, 25:1, 50:1, 100:1, 200:1, 250:1 or 500:1.

The compounds of the present invention may be synthesized, for example, in accordance with the reaction scheme shown in Figure 2. Ketone (**6'**) may be converted to amine (**7'**) via reductive amination. Amine (**7'**) may then be coupled to the butylated hydroxyanisole ester of 4-flurobenzoic acid to provide ester (**8'**). The BHA group may be removed and then the corresponding acid converted to amide, for example via an activated ester such as a BOP ester, using the amine NHR_aR_b, to provide N-methyl derivative (**9'**). The N-methyl group may then be replaced by an R_1 group by treatment with phenyl chloroformate followed by hydrolysis of the resulting carbamate. N-alkylation with an alkylating agent of the formula R_1-X, where X is a halogen atom, provides inventive compound (**5**). For specific examples of synthesis of the inventive compounds, see the Examples below.

The compounds may be in the form of a pharmaceutically acceptable salt via protonation of the amine(s) with a suitable acid, i.e., a pharmaceutically acceptable acid. The acid may be an inorganic acid or an organic acid. Suitable acids include, for example,

hydrochloric, hydroiodic, hydrobromic, sulfuric, phosphoric, citric, acetic and formic acids.

The compounds of the present invention may be used to bind opioid receptors. Such binding may be accomplished by contacting the receptor with an effective amount of the inventive compound. Of course, such contacting is preferably conducted in a aqueous medium, preferably at physiologically relevant ionic strength, pH, etc.

The inventive compounds may also be used to treat patients having disease states which are ameliorated by binding opioid receptors. Such diseases states include heroin addiction, pain, i.e., the compounds are used as analgesics. The compounds of the inventive may also be used to reverse mu-induced respiratory depression, as cytostatica agents, as antimigraine agents, as immunomodulators, as immunosuppressives, as antiarthritic agents, as antiallergic agents, as virucides, to treat diarrhea, as antidepressants, as uropathic agents, as antitussives, as antiadditive agents, as anti-smoking agents, to treat alcoholism, as hypotensive agents, or to treat obesity.

The compounds may be administered in an effective amount by any of the conventional techniques well-established in the medical field. For example, the compounds may be administered orally, intraveneously, or intramuscularly. When so administered, the inventive compounds may be combined with any of the well-known pharmaceutical carriers and additives that are customarily used in such pharmaceutical compositions. For a discussion of dosing forms, carriers, additives, pharmacodynamics, etc., see Kirk-Othmer Encyclopedia of Chemical Technology, Fourth Edition, Vol. 18, 1996, pp. 480-590, incorporated herein by reference. The patient is preferably a mammal, with human patients especially preferred.

EXAMPLES

Having generally described this invention, a further understanding can be obtained by reference to certain specific examples which are provided herein for purposes of illustration only and are not intended to be limiting unless otherwise specified.

Chemistry

Preparation of **5a-d** (Figure 3) began with reductive amination of 3-tropanone (**6**) with 3-methoxyaniline using titanium (IV) isopropoxide[9] which gave **7** as a single diastereomer (*endo* based on the observations of Abdel-Magid et al.)[10] in 38% yield. This intermediate was then coupled to the butylated hydroxyanisole (BHA) ester of 4-fluorobenzoic acid to

give **8** in 83% yield.[11] Removal of the BHA group was accomplished by trans-esterification with refluxing sodium methoxide in toluene/N-methylpyrrolidinone followed by saponification of the methyl ester. The zwitterionic intermediate was isolated as a slurry of its HCl salt and converted without purification into the diethylamide using benzotriazol-1-yl-oxy-tris-(dimethylamino) phosphonium hexafluorophosphate (BOP a.k.a. Castro's reagent), diethylamine, and triethylamine in a tetrahydrofuran (THF) slurry to give **9** in 78% yield. Conversion to the appropriately N-substituted analog was accomplished by treating **9** with phenyl chloroformate followed by hydrolysis of the resulting carbamate with potassium hydroxide in isopropyl alcohol. N-Alkylation with the appropriate alkyl bromide then gave **5a-c**. Compound **5d** was prepared from **5a** in 77% yield by treatment with boron tribromide.

Biological Data

The binding affinities of **5a-d** and the reference compounds SNC-80 (**2**) and (-)-RTI-5989-54 (**3**) for the μ, δ, and κ opioid receptors were determined using competitive binding assays following previously reported procedures[6,7] (Table 1). Determination of agonism was accomplished by measuring the stimulation of binding of the GTP analog [^{35}S]GTP-γ-S in guinea pig caudate elicited by the test compounds (Table 2).[6,7] The receptor responsible for any observed agonist activity was determined by measuring stimulation in the presence of selective antagonists. Measures of antagonism for the three opioid receptors were obtained by monitoring the test compounds ability to inhibit stimulation produced by the selective agonists DAMGO (μ), SNC-80 (δ), and U69,593 (κ) (Table 3).[6,7]

Results and Discussion

The radioligand binding data for the compounds **5a-d** along with comparative data for SNC-80 (**2**) and the piperidine derivative **3** are shown in Table 1. As is apparent, the tropane analogs **5a-d** all display excellent affinity for the delta opioid receptor versus the mu or kappa receptors and possess higher affinity for delta relative to the piperidine **3** but less affinity than the piperazine **2**. This translates into higher degrees of selectivity for the tropane derivatives relative to the piperidine derivative **3**. Moreover, unlike the piperidine compounds in general, the selectivity evident in the tropane analogs rivals that found in SNC-80 (**2**). Compound **5d** demonstrates that analogs possessing an aryl hydroxy substituent produce higher affinity and lower selectivity relative to the corresponding methyl ether

derivatives like **5a**. Similar behavior was found for transitions between **1** and **2**; however, in this series, the methyl ether compounds are generally more selective.[2]

Inspection of Table 2 reveals that the tropane analogs **5a-c** all exhibit selective delta opioid stimulation of GTP binding but that this stimulation diminishes as the size of the N-substituent increased. Thus, the N-allyl analog **5a** has 41% stimulation, whereas the N-prenyl analog **5c** shows only 28% stimulation. Surprisingly, compound **5d**, which is highly selective for the delta receptor in the binding assay, is totally unselective in the [^{35}S]GTP-γ-S efficacy assay showing 44 to 47% stimulation at the μ, δ, and κ opioid receptors respectively (Table 2). Thus, changing a methoxy substituent (**5a**) to a hydroxy substituent (**5d**) results in complete loss of selectivity in the efficacy screen. It is apparent that selectivity in binding does not necessarily translate into selectivity in functional assays. This stands in contrast to the piperidine-based compound **3** which demonstrated full agonist activity in similar assays with an observed K_d equivalent to that found for **2**.[7] Thus, compared with similarly functionalized piperidine-based ligands, the more rigid tropane analogs demonstrate dramatically lower ability to stimulate GTP-γ-S binding.

Table 1. Radioligand Binding Results at the μ, δ, and κ Opioid Receptors

	K_i (nM ± SD)			
	μ	δ	κ	
Compound	[^{3}H]DAMGO[a]	[^{3}H]DADLE[b]	[^{3}H]U69,593[c]	μ/δ
2, SNC-80	1614 ± 131	1.57 ± 0.19	3535 ± 1841	1028
3, (-)-RTI5989-54	2623±307	5.85±0.31	1448±196	448
5a	2547 ± 344	3.28 ± 0.31	1076 ± 84	776
5b	>3400	3.7±0.16	1166±99	>918
5c	1105±114	3.51±0.32	788±45	315
5d	686 ± 94	1.26 ± 0.08	73 ± 7.7	544

[a] [^{3}H]DAMGO [(D-Ala^2,MePhe^4,Gly-ol^5)enkephalin]. Tritiated ligand selective for μ opioid receptor.

[b] [^{3}H]DADLE [(D-Ala^2,D-Leu^5)enkephalin]. Tritiated ligand selective for δ opioid receptor.

[c] [^{3}H]U69,593 {[^{3}H](5α,7α,8β)-(-)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro[4,5]-dec-8-yl]benzeneacetamide}. Tritiated ligand selective for κ opioid receptor.

Table 2. % Stimulation of [^{35}S]GTP-γ-S Binding by DAMGO, SNC-80, U69,593, and Compounds **5a-d** (10 μM) in Guinea Pig Caudate Membranes

	Unblocked Condition % Stimulation (mean ± SD)	μ_ Condition % Stimulation (mean ± SD)[a]	δ_ Condition % Stimulation (mean ± SD)[b]	κ Condition % Stimulation (mean ± SD)[c]
DAMGO	115 ± 10	90 ± 10	8.6 ± 1.2	6 ± 5
SNC-80 (**2**)	102 ± 7	1.9 ± 1.7	105 ± 2	4 ± 3
U69,593	148 ± 7	34 ± 5	30 ± 3	103 ± 25
5a	46 ± 3	0	41 ± 4	0
5b	37 ± 8	0	33 ± 2	0
5c	29 ± 5	0	28 ± 13	0
5d	79 ± 9	44 ± 2	40 ± 3	47 ± 18

[a]The μ-selective condition used 20 nM naltrindole (NTI, antagonist selective for δ opioid receptor) and 6 nM nor-Binaltorphimine (nor-BNI, antagonist selective for κ opioid receptor).

[b]The δ-selective condition used 6000 nM CTAP (antagonist selective for mu opioid receptor) and 6 nM nor-BNI.

[c]The κ-selective condition used 6000 nM CTAP and 20 nM NTI.

In Table 3, the data listed show the antagonist activity of the tropane analogs **5a-d**. Across the series of methoxy substituted compounds **5a-c**, the antagonist activity is observed to increase with the size of the N-substituent. As noted above, it was across the same series (**5a-c**) that stimulation of GTP binding was found to decrease. Thus, taken together, the trend in the data clearly suggests that further manipulation of the N-substituent could lead to more potent delta antagonists with diminished agonist activity. The aryl hydroxy substituted compound **5d** demonstrates an even greater degree of antagonist activity than the similarly substituted methoxy derivative **5a**. This observation is in line with expectations since typical opioid antagonists display greater activity with hydroxyl groups relative to methoxy groups.[12] For comparison, compound **3** does not inhibit SNC-80 stimulated GTP binding at a concentration of 10 μM.[6,7] Overall, the data available from this study reveal that reorganization of ring alkyl substituents

and increasing rigidity can minimize agonist activity and promote antagonist activity.

Table 3. % Inhibition of DAMGO, SNC-80, and U69,593 (10 μM)-Stimulated [^{35}S]GTP-γ-S Binding by Compounds **5a-d** in Guinea Pig Caudate Membranes

Compound	% Inhibition of DAMGO-Stimulated [^{35}S]GTP-γ-S Binding	% Inhibition of SNC-80-Stimulated [^{35}S]GTP-γ-S Binding	% Inhibition of U69,593-Stimulated [^{35}S]GTP-γ-S Binding
5a	0	25%	0
5b	0	49%	0
5c	25%	69%	23%
5d	0	34%	0

Experimental

α-3-(N-3-Methoxyanilino)tropane (6). N-Methyltropanone (12.0 g, 86.2 mmol) and *m*-anisidine (10.4 mL, 94.8 mmol) were mixed in neat titanium (IV) isopropoxide (31.8 mL, 107.8 mmol) and stirred under nitrogen for 24 h. Ethanol (anhydrous, 100 mL) was added followed by the careful addition of $NaBH_4$ (6.5 g, 172.4 mmol). The reaction mixture was stirred for 30 min and quenched with 1 N NaOH. The resulting mixture was filtered through celite, washing with ether (2 x 100 mL) followed by CH_2Cl_2 (2 x 100 mL). The organic layer was collected, dried (Na_2SO_4) and solvent removed under reduced pressure yielding crude product. Crude product was purified by flash chromatography ($CHCl_3$:CH_3OH:NH_4OH, 80:18:2,) to 7 (8.2 g, 38%) as a brown solid: mp = 69-72 °C; ^{1}H-NMR ($CDCl_3$) δ 7.07 (t, 1H, J = 8.1 Hz), 6.24 (d, 1H, J = 8.2), 6.14 (d, 1H, J = 8.1), 6.07 (s, 1H), 3.91 (d, 1H, J = 5.9), 3.76 (s, 3H), 3.58 (m, 1H), 3.13 (m, 2H), 2.29 (s, 3H), 2.23-2.15 (m, 3H), 2.12-1.98 (m, 2H), 1.74 (d, 2H, J = 13.7 Hz); ^{13}C-NMR ($CDCl_3$) δ 161.3, 149.0, 130.3, 106.5, 102.3, 99.2, 60.5, 55.4, 44.6, 40.7, 36.6, 26.2. Anal. ($C_{15}H_{22}N_2O$) C, H, N.

4-[((8-methyl-8-azabicyclo[3.2.1]octyl-3-yl)-3-methoxyanilino)-2,6-ditertbutyl-4-hydroxyphenyl]benzoate (7). α-3-(N-3-Methoxyanilino)tropane (2.00 g, 8.12 mmol) was dissolved in dry THF(7.5 mL) and dry HMPA (3 mL) and cooled to –42 °C. A 1.6 M solution of *n*-BuLi (5.58 mL, 8.93 mmol) was slowly added and the reaction mixture was allowed to warm to 0 °C. The mixture was cannulated into a solution of 2,6-di-*tert*-butyl-4-methoxyphenyl 4-fluorobenzoate (2.91 g, 8.12 mmol)) in dry THF (7.5 mL) and dry HMPA (3 mL) at room temperature and heated at 50 °C for 4 h. The reaction mixture was cooled to room temperature then quenched with 20% NH_4Cl solution (50 mL) and made basic (pH = 14) with 2 M NaOH. The aqueous layer was extracted with ether (3 x 50 mL), organic layer collected, dried (Na_2SO_4) and solvent removed under reduced pressure yielding crude product. Crude product was purified by flash chromatography ((50% $CHCl_3$:CH_3OH:NH_4OH, 80:18:2) in $CHCl_3$) to afford **8** (3.9 g, 83%) as an off-white solid: mp = 208-211 °C; ^{1}H-NMR ($CDCl_3$) δ 7.94 (d, 2H, J = 8.9 Hz), 7.35 (t, 1H, J = 8.0 Hz), 6.92 (d, 1H, J = 8.5 Hz), 6.88 (s, 2H), 6.68 (d, 1H, J = 7.9 Hz), 6.64 (s, 1H), 6.62 (d, 2H, J = 8.9), 4.54 (m, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.21 (br., 2H), 2.53 (m, 2H), 2.16 (s, 3H), 2.05 (m, 2H), 1.30 (s, 18H), 1.24-1.09 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 167.5, 161.2, 156.4, 153.4, 144.2, 142.5, 132.2, 130.8, 123.6, 118.4, 117.1, 113.5, 113.2, 111.8, 59.5, 55.7, 55.6, 48.9, 41.3, 36.7, 36.0, 31.8, 29.8. Anal. ($C_{37}H_{48}N_2O_4$) C, H, N.

4-[(8-Methyl-8-azabicyclo[3.2.1]octyl-3-yl)-3-methoxyanilino]-N,N-diethylbenzamide(9). A solution of **8** (5.00 g, 8.54 mmol) in dry toluene (75 mL) and NMP (20 mL) was added to freshly prepared sodium methoxide (9.2 g, 170 mmol) and refluxed for 5 h. Toluene was removed under reduced pressure, the residue was dissolved in 12:1 EtOH/H_2O (100 mL) and refluxed for 1 h. Alcohol was removed under reduced pressure and resulting residue was taken up in water (300 mL) and extracted with hexanes (3 x 100 mL). The aqueous layer was made acidic (pH = 1) with 3 M HCl and extracted with 3:1 CH_2Cl_2/THF (6 x 200 mL). The organic layer was collected, dried (Na_2SO_4) and solvent removed under reduced pressure yielding impure acid. This was slurried in THF (100 mL), triethylamine (60 mL) and diethylamine (17.7 mL). BOP reagent (3.77 g, 8.54 mmol) was added and the reaction mixture was stirred for 2 days at room temperature. The reaction mixture was diluted with ether (300 mL), washed with water (4 x 100 mL) and with a saturated solution of $NaHCO_3$ (100 mL). The organic layer was collected, dried (Na_2SO_4) and solvent removed under reduced pressure yielding crude product as a dark brown oil. This was purified by flash ((40% $CHCl_3$:CH_3OH:NH_4OH, 80:18:2) in

$CHCl_3$) to afford **9** (2.82 g, 78%). ^{1}H-NMR ($CDCl_3$) δ 7.23 (m, 3H), 6.73 (m, 3H), 6.55 (m, 2H), 4.40 (m, 1H), 3.77 (s, 3H), 3.42 (br., 4H), 3.18 (br., 2H), 2.45 (m, 2H), 2.16 (s, 3H), 2.02 (m, 2H), 1.32-1.24 (m, 4H), 1.17 (t, 6H, J = 7.0); ^{13}C-NMR ($CDCl_3$) δ 171.8, 160.9, 149.9, 147.1, 130.3, 128.4, 128.0, 121.4, 118.7, 114.3, 110.3, 59.7, 55.5, 48.8, 41.7 (br.), 41.2, 36.2, 29.3, 13.9 (br.). Anal. ($C_{26}H_{35}N_3O_2 \cdot 1.25\ H_2O$) C, H, N.

4-[(8-Allyl-8-azabicyclo[3.2.1]octyl-3-yl)-3-methoxyanilino]-N,N-diethylbenzamide (5a). Compound **9** (2.25 g, 5.33 mmol) was treated with phenyl chloroformate (2.67 mL, 21.32 mmol) in dry CH_2Cl_2 (50 mL) at room temperature for 2 h. The reaction was quenched with 1 M NaOH (50 mL) then extracted with $CHCl_3$ (3 x 25 mL). The organic layer was collected, dried (Na_2SO_4) and solvent removed under reduced pressure yielding crude product. This was purified by flash chromatography (15% ($CHCl_3$:CH_3OH:NH_4OH, 80:18:2) in $CHCl_3$)) to afford phenyl carbamate (2.3 g, 83%) and unreacted starting material (320 mg, 14%). The carbamate (2.3 g, 4.45 mmol) was dissolved in methanol (75 mL), water (50 mL), isopropanol (30 mL) and 50% NaOH (20 mL) then refluxed for 20 h. The alcohol was removed under reduced pressure and aqueous phase extracted with 3:1 CH_2Cl_2:THF (6 x 150 mL). The organic layer was collected, dried (Na_2SO_4) and solvent removed under reduced pressure yielding crude product. This was purified by flash chromatography ((15% $CHCl_3$:CH_3OH:NH_4OH, 80:18:2) in $CHCl_3$) to afford 4-[(8-azabicyclo[3.2.1]octyl-3-yl)-3-methoxyanilino]-N,N-diethylbenzamide (880 mg, 75%, after correction for recovered starting carbamate) and phenyl carbamate starting material (800 mg, 35%). ^{1}H-NMR ($CDCl_3$) δ 7.26 (m, 3H), 6.72 (m, 3H), 6.58 (m, 2H), 4.39 (m, 1H), 3.76 (s, 3H), 3.60 (br., 2H), 3.42 (br., 4H), 2.42 (m, 3H), 1.72 (m, 2H), 1.54 (m, 2H) 1.30-1.22 (m, 2H), 1.17 (t, 6H, J = 7.0); ^{13}C-NMR ($CDCl_3$) δ 171.8, 160.9, 149.7, 146.9, 130.4, 128.4, 128.1, 120.3, 118.7, 113.9, 110.4, 55.5, 52.6, 48.8, 41.7 (br.), 35.2, 33.5, 13.9 (br.).

A solution of this material (490 mg, 1.20 mmol) in ethanol (10 mL) was reacted at room temperature with K_2CO_3 (331 mg, 2.40 mmol) and allyl bromide (0.114 mL, 1.32 mmol) for 2 days. The alcohol was removed under reduced pressure and solid material dissolved in water (25 mL). The aqueous phase was extracted with $CHCl_3$ (3 x 100 mL), organic layer collected, dried (Na_2SO_4) and solvent removed under reduced pressure yielding crude product. This was purified by flash chromatography (25% ($CHCl_3$:CH_3OH:NH_4OH, 80:18:2) in $CHCl_3$) to afford **5a** (434 mg, 81%) as an off-white foam. ^{1}H-NMR ($CDCl_3$) δ 7.26 (m, 3H), 6.75 (m, 3H), 6.55

(m, 2H), 5.14 (m, 2H), 4.45 (m, 1H), 3.77 (s, 3H), 3.43 (br., 4H), 3.29 (br., 2H), 2.89 (d, 2H, J = 6.0 Hz), 2.45 (m, 2H), 1.93 (m, 2H), 1.44 (d, 2H, J = 7.5 Hz)) 1.29 (m, 2H), 1.17 (t, 6H, J = 7.0); ^{13}C-NMR ($CDCl_3$) δ 171.8, 160.9, 149.9, 147.4, 136.8, 130.3, 128.3, 128.2, 120.2, 119.1, 116.9, 113.7, 110.3, 57.5, 55.9, 52.6, 49.0, 41.2 (br.), 36.1, 29.4, 13.9 (br.). Anal. ($C_{28}H_{37}N_3O_2 \cdot HCl \cdot 0.5\ H_2O$) C, H, N

4-[(8-*cis*-Crotyl-8-azabicyclo[3.2.1]octyl-3-yl)-3-methoxyanilino]-N,N-diethylbenzamide: (5b). A solution of the (Z)-crotyl mesylate (60.8 mg, 0.41 mmol) in dry THF (10 mL) was added dropwise to a solution of 4-[(8-azabicyclo[3.2.1]octyl-3-yl)-3-methoxyanilino]-N,N-diethylbenzamide (150 mg, 0.37 mmol) and triethylamine (0.10 mL, 0.72 mmol) in dry THF (10 mL) at 0 °C under N_2. The reaction was allowed to warm to room temperature and then quenched with sat. $NaHCO_3$. Aqueous layer extracted with CH_2Cl_2 (3 x 50 mL), organic layer collected, dried (Na_2SO_4) and solvent removed under reduced pressure yielding crude product. Crude product was purified by flash chromatography (25% ($CHCl_3$:MeOH:NH_4OH, 80:18:2) in $CHCl_3$ CMA80) to **5b** (118 mg, 70%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ 7.27 (m, 3H), 6.82 (d, 2H, J = 8.5 Hz), 6.74 (d, 1H, J = 8.2 Hz), 6.65 (d, 1H, J = 8.8 Hz), 6.60 (s, 1H), 5.64 (m, 2H), 4.47 (m, 1H), 3.80 (s, 3H), 3.45 (br. 4H), 3.36 (br. 2H), 3.01 (d, 2H, J = 5.3 Hz), 2.53 (m, 2H), 1.64 (d, 3H. J = 5.5 Hz), 1.59 (d, 2H, J = 7.7 Hz), 1.42 (m, 2H), 1.21 (t, 6H, J = 6.9 Hz); ^{13}C-NMR ($CDCl_3$) δ 172.9, 162.0, 151.2, 148.9, 131.5, 129.9, 129.3, 129.1, 128.4, 121.3, 120.8, 114.9, 111.5, 58.9, 56.7, 50.2, 50.1, 43.5, 37.0, 30.3, 15.1 (br.), 14.6.

4-[(8-Prenyl-8-azabicyclo[3.2.1]octyl-3-yl)-3-methoxyanilino]-N,N-diethylbenzamide(5c). A solution of 4-[(8-azabicyclo[3.2.1]octyl-3-yl)-3-methoxyanilino]-N,N-diethylbenzamide (475 mg, 1.16 mmol) in ethanol (10 mL) was stirred at room temperature with K_2CO_3 (320 mg, 2.32 mmol) and prenyl bromide (0.147 mL, 1.28 mmol) for 2 days. The alcohol was removed under reduced pressure and solid material dissolved in water (25 mL). The aqueous phase was extracted with $CHCl_3$ (3 x 100 mL), organic layer collected, dried (Na_2SO_4) and solvent removed under reduced pressure yielding crude product. This was purified by flash chromatography (25% ($CHCl_3$:MeOH:NH_4OH, 80:18:2) in $CHCl_3$ CMA80) to **5c** (421 mg, 76%) as a yellow oil. ^{1}H-NMR ($CDCl_3$) δ 7.23 (m, 3H), 6.78 (d, 2H, J = 8.1 Hz), 6.70 (d, 1H, J = 8.2 Hz) 6.61 (d, 1H, J = 8.0 Hz), 6.56 (s, 1H), 5.30 (br., 1H), 4.43 (m, 1H), 3.77 (s, 3H), 3.42 (br., 4H), 3.30 (br., 2H), 2.89 (br., 2H), 2.47 (m, 2H), 1.96 (m, 2H), 1.75 (s, 3H), 1.60 (s,

3H), 1.53 (m, 2H), 1.37 (m, 2H), 1.17 (t, 6H, J = 6.9); ^{13}C-NMR ($CDCl_3$) δ 171.8, 160.9, 150.0, 147.7, 135.0, 130.3, 128.4, 128.2, 122.5, 120.2, 119.5, 113.7, 110.3, 57.5, 55.6, 50.4, 49.0, 41.8 (br.), 35.9, 29.3, 26.2, 18.4, 13.9 (br.). Anal. ($C_{30}H_{41}N_3O_2 \cdot HCl \cdot H_2O$) C, H, N

4-[(8-Allyl-8-azabicyclo[3.2.1]octyl-3-yl)-3-hydroxyanilino]-N,N-diethylbenzamide (5d). To a solution of **5a** (150 mg, 0.34 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C was added BBr_3 (0.158 mL, 1.68 mmol) dropwise over 5 min. The reaction mixture was allowed to warm to room temperature then quenched with H_2O (20 mL). Aqueous layer extracted with CH_2Cl_2 (2 x 25 mL), organic layer collected, dried (Na_2SO_4) and solvent removed under reduced pressure yielding crude product. Crude product was purified by flash chromatography ((50% $CHCL_3$:CH_3OH:NH_4OH, 80:18:2) in $CHCl_3$) to afford **5d** (112 mg, 77%) as an off-white foam. ^{1}H-NMR ($CDCl_3$) δ 7.24 (m, 2H), 7.04 (d, 2H, J = 8.6 Hz), 6.80 (d, 1H, j = 8.1 Hz), 6.45 (m, 4H), 5.93 (m, 1H), 5.13 (m, 2H), 4.35 (m, 1H), 3.37 (br., 2H), 3.30 (br., 4H), 2.91 (d, 2H, J = 6.1 Hz), 2.36 (m, 2H), 1.93 (m, 2H), 1.41 (d, 2H, J = 7.7 Hz), 1.25 (m, 2H), 1.14 (br., 6H); ^{13}C-NMR ($CDCl_3$) δ 172.4, 158.8, 150.6, 145.3, 135.7, 130.7, 128.4, 125.8, 121.0, 118.1, 117.2, 115.8, 114.3, 57.3, 55.9, 48.0, 42.0 (br.), 36.0, 29.4, 13.9 (br.). Anal. ($C_{27}H_{35}N_3O_2 \cdot HCl \cdot 0.25$ H_2O) C, H, N

[^{35}S]GTPγS Assay Conditions

[^{35}S]GTP-γ-S binding was determined as described previously. Briefly, test tubes received the following additions: 50 µl buffer A (50 mM Tris-HCl, pH 7.4, containing 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA), 50 µl GDP in buffer A (FC = 100 µM), 50 µl drug in buffer A, 50 µl [^{35}S]GTP-γ-S in buffer A (FC =45 pM), and 300 µl of guinea pig caudate membranes in buffer B (FC=50 mM Tris-HCl, pH 7.4, containing 100 mM NaCl, 10 mM $MgCl_2$, 1 mM EDTA, 1 mM DTT, 0.1% BSA). Incubations proceeded for 3 h at 25 ° C (steady state) in a final volume of 0.5 mL. Nonspecific binding was determined using GTP-γ-S (FC = 40 µM). Bound and free [^{35}S]GTP-γ-S was separated by vacuum filtration through GF/B filters. The filters were punched into the vials to which was added 5 mL LSC-cocktail and counted in a liquid scintillation counter. The results are mean ± SD from three experiments, each performed in duplicate determinations.

Table of Elemental Analyses

Compound	% Calculated (C, H, N)	% Found (C, H, N)
7	73.13, 9.00, 11.37	72.91, 8.96, 11.38
8	75.99, 8.27, 4.79	75.90, 8.25, 4.79
9	70.32, 8.51, 9.46	70.32, 8.09, 9.38
5a	68.20, 7.97, 8.52	67.98, 7.93, 8.25
5b	69.93, 8.24, 9.41	69.66, 8.31, 9.31
5c	67.97, 8.37, 7.93	67.81, 8.03, 7.69
5d	68.34, 7.75, 8.85	68.45, 7.68, 8.66

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced otherwise than as specifically described herein.

References

1. Chang, K. J.; Rigdon, G. C.; Howard, J. L.; McNutt, R. W. *J. Pharm. Exp. Ther.* **1993**, *267*, 852.

2. Calderon, S. N.; Rothman, R. B.; Porreca, F.; Flippen-Anderson, J. L.; McNutt, R. W.; Xu, H.; Smith, L. E.; Bilsky, E. J.; Davis, P.; Rice, K. C. *J. Med. Chem.* **1994**, *37*, 2125.

3. Dondio, G.; Ronzoni, S.; Petrillo, P. *Exp. Opin. Ther. Patents* **1999**, *9*, 353.

4. Zhang, X.; Rice, K. C.; Calderon, S., N.; Kayakiri, H.; Smith, L., Coop, Andrew; Jacobson, A. E.; Rothman, R. B.; Davis, P.; Dersch, C. M.; Porreca, F. *J. Med. Chem.* **1999**, *42*, 5455.

5. Dondio, G.; Ronzoni, S.; Eggleston, D. S.; Artico, M.; Petrillo, P.; Petrone, G.; Visentin, L.; Farina, C.; Vecchietti, V.; Clarke, G. D. *J. Med. Chem.* **1997**, *40*, 3192.

6. Thomas, J. B.; Herault, X. M.; Rothman, R. B.; Burgess, J. P.; Mascarella, S. W.; Xu, H.; Horel, R. B.; Dersch, C. M.; Carroll, F. I. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3053.

7. Thomas, J. B.; Atkinson, R. N.; Herault, X. M.; Rothman, R. B.; Mascarella, S. W.; Dersch, C. M.; Xu, H.; Horel, R. B.; Carroll, F. I. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3347.

8. Su, Y.-F.; McNutt, R. W.; Chang, K.-J. *J. Pharmacol. Exp. Ther.* **1998**, *287*, 1.

9. Mattson, R. J.; Pham, K. M.; Leuck, D. J.; Cowen, K. A. *J. Org. Chem.* **1990**, *55*, 2552.

10. Abdel-Magid, A. F.; Carson, K., G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849.

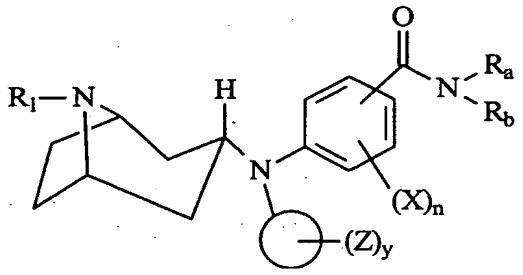
11. Hattori, T.; Satoh, T.; Miyano, S. *Synthesis* **1996**, 514.

12. Aldrich, J. V. In *Burger's Medicinal Chemistry and Drug Discovery*; M. E. Wolff, Ed.; John Wiley & Sons: New York, 1996; Vol. 3.

The references cited above are incorporated herein by reference.

CLAIMS

1. A compound represented by formula:



wherein

R_a and R_b are each, independently, hydrogen, an alkyl group or an alkenyl group, or R_a and R_b are bonded together to form an alkyl group;

each X is, independently, an alkyl group;

o is a five- or six-membered aryl or heteroaryl group;

each Z is, independently, an alkyl group, -OH, -OR, halogen, $-CF_3$, -CN, $-NH_2$, -NHR, or $-N(R)_2$;

each R is, independently, an alkyl group, an alkenyl group, an aryl group, or an alkaryl group;

n is 0 or an integer from 1 to 4;

y is 0 or an integer from 1 to 5; and

R_1 is an alkyl group, an alkenyl group, or an aralkyl group;

or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1, wherein

R_a and R_b are each, independently, an alkyl group or an alkenyl group, or R_a and R_b are bonded together to form an alkyl group;

the -NC(O)-NRaRb moiety is bonded to the adjacent phenyl ring at the 3- or 4-position;

o is a five- or six-membered aryl or heteroaryl group;

each Z is, independently, an alkyl group, -OH, -OR, halogen, $-CF_3$, -CN, $-NH_2$, -NHR, or $-N(R)_2$;

each R is, independently, an alkyl group, an alkenyl group, an aryl group, or an alkaryl group;

n is 0;

y is 0, 1 or 2; and

R_1 is an alkyl group, an alkenyl group, or an aralkyl group;

or a pharmaceutically acceptable salt thereof.

3. The compound of Claim 2, wherein

R_a and R_b are each, independently, an alkyl group, or R_a and R_b are bonded together to form an alkyl group;

o is a phenyl group;

Z is an alkyl group, -OH, -OR, halogen, $-CF_3$, -CN, $-NH_2$, -NHR, or $-N(R)_2$;

each R is, independently, an alkyl group, an alkenyl group, an aryl group, or an alkaryl group;

y is 1; and

R_1 is an alkenyl group;

or a pharmaceutically acceptable salt thereof.

4. The compound of Claim 3, wherein

Z is an alkyl group, -OH, or -OR; and

R is an alkyl group or an alkenyl group;

or a pharmaceutically acceptable salt thereof.

5. The compound of Claim 4, wherein

Z is -OH or -OR; and

R is an alkyl group;

or a pharmaceutically acceptable salt thereof.

6. The compound of Claim 1, wherein

each alkyl group, independently, contains 1 to 8 carbon atoms;

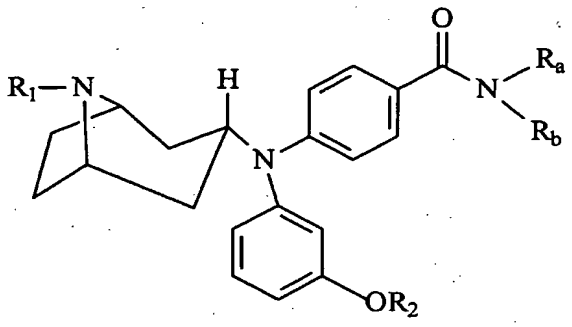
each alkenyl group, independently, contains 3 to 8 carbon atoms;

each alkaryl group, independently, contains 7 to 12 carbon atoms;

each aryl group, independently, contains 6 to 20 carbon atoms; and

each heteroaryl group, independently, contains 5 to 20 carbon atoms.

7. The compound of Claim 1, which is represented by the formula:



wherein

R_a and R_b are each, independently, an alkyl group, or R_a and R_b are bonded together to form an alkyl group;

R_2 is hydrogen or an alkyl group;

R_1 is an alkenyl group;

or a pharmaceutically acceptable salt thereof.

8. The compound of Claim 7, wherein R_a and R_b are each, independently, an alkyl group.

9. The compound of Claim 7, wherein

each alkyl group, independently, contains 1 to 8 carbon atoms; and

each alkenyl group, independently, contains 3 to 8 carbon atoms.

10. The compound of Claim 7, wherein

R_a and R_b are each ethyl;

R_2 is hydrogen or methyl; and

R_1 is allyl, crotyl or prenyl.

11. The compound of Claim 1, which is a pharmaceutically acceptable salt of a pharmaceutically acceptable acid.

12. The compound of Claim 11, wherein the pharmaceutically acid is selected from the group consisting of hydrochloric acid, hydroiodic acid, hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, acetic acid and formic acid.

13. A pharmaceutical composition, comprising the compound of Claim 1 and a pharmaceutically acceptable carrier or diluent.

14. A method of binding opioid receptors, comprising administering an effective amount of the compound of Claim 1 to a mammalian subject in need thereof.

15. The method of Claim 14, wherein the subject is a human.

16. A method of binding opioid receptors, comprising administering an effective amount of the composition of Claim 13 to a mammalian subject in need thereof.

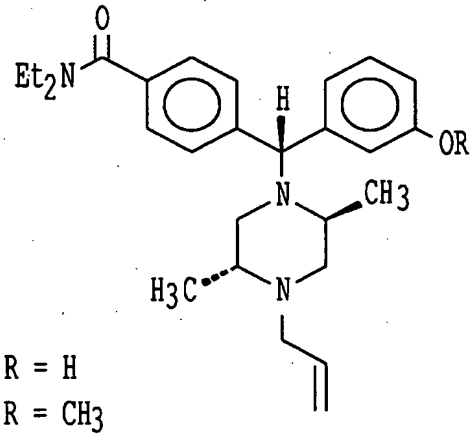
17. The method of Claim 16, wherein the subject is a human.

18. A method of binding δ-opioid receptors, comprising administering an effective amount of the compound of Claim 1 to a mammalian subject in need thereof.

19. The method of Claim 18, wherein the subject is a human.

20. A method of binding δ-opioid receptors, comprising administering an effective amount of the composition of Claim 13 to a mammalian subject in need thereof.

21. The method of Claim 20, wherein the subject is a human.



1: R = H
2: R = CH_3

FIG. 1A

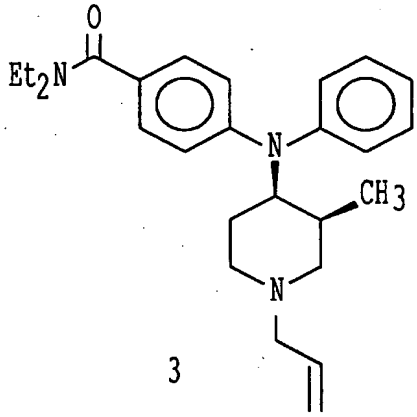


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FIG. 1B

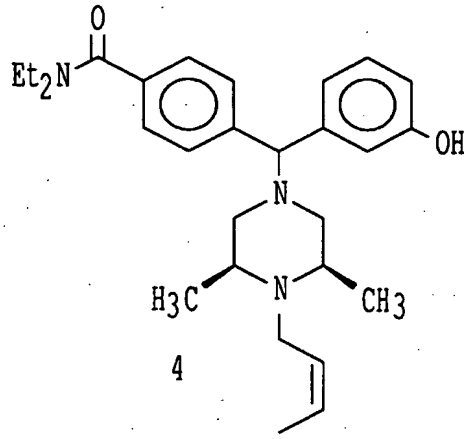

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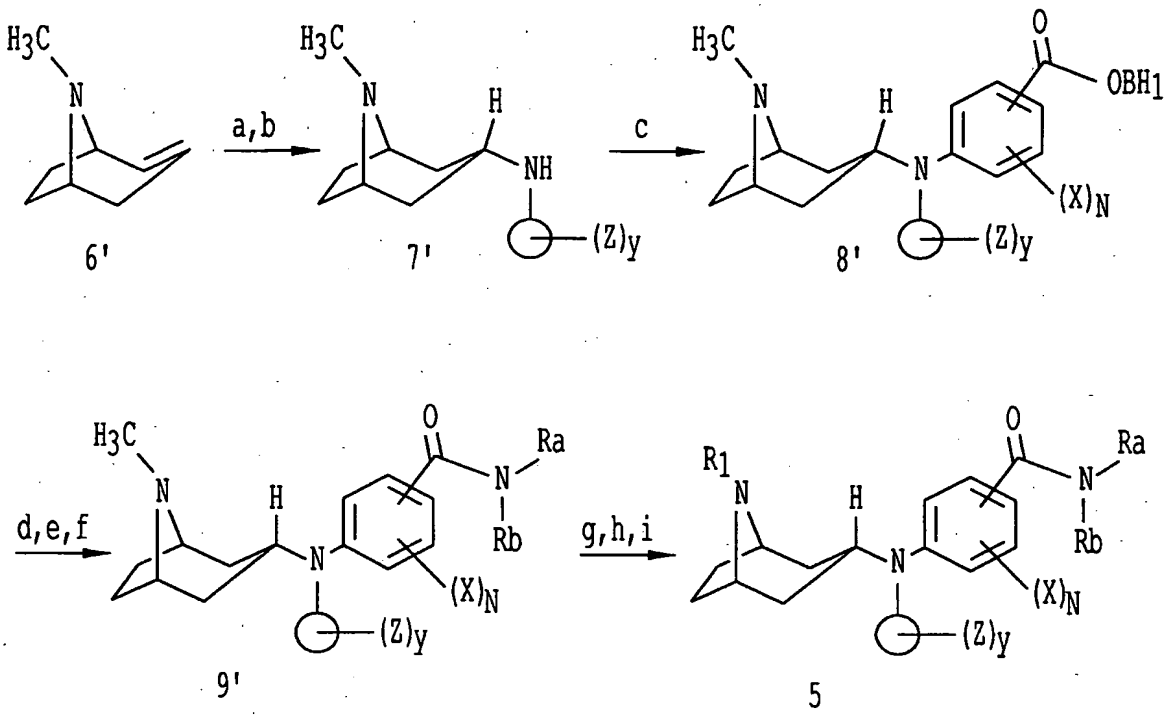
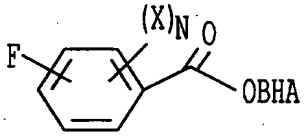
FIG. 1C



(a) $Ti(O\text{-}iPr)_4$, H_2N-(Z)y

(b) $NaBH_4$

(c) N-BuLi; HMPA + 

(d) N-methylpyrrolidinone, $NaOCH_3$

(e) EtOH, H_2O

(f) RaRbNH, BOP, Et_3N

(g) PhOCOCl

(h) KOH, i-PrOH, H_2O

(i) R_1-X

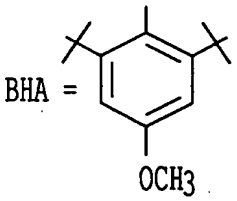
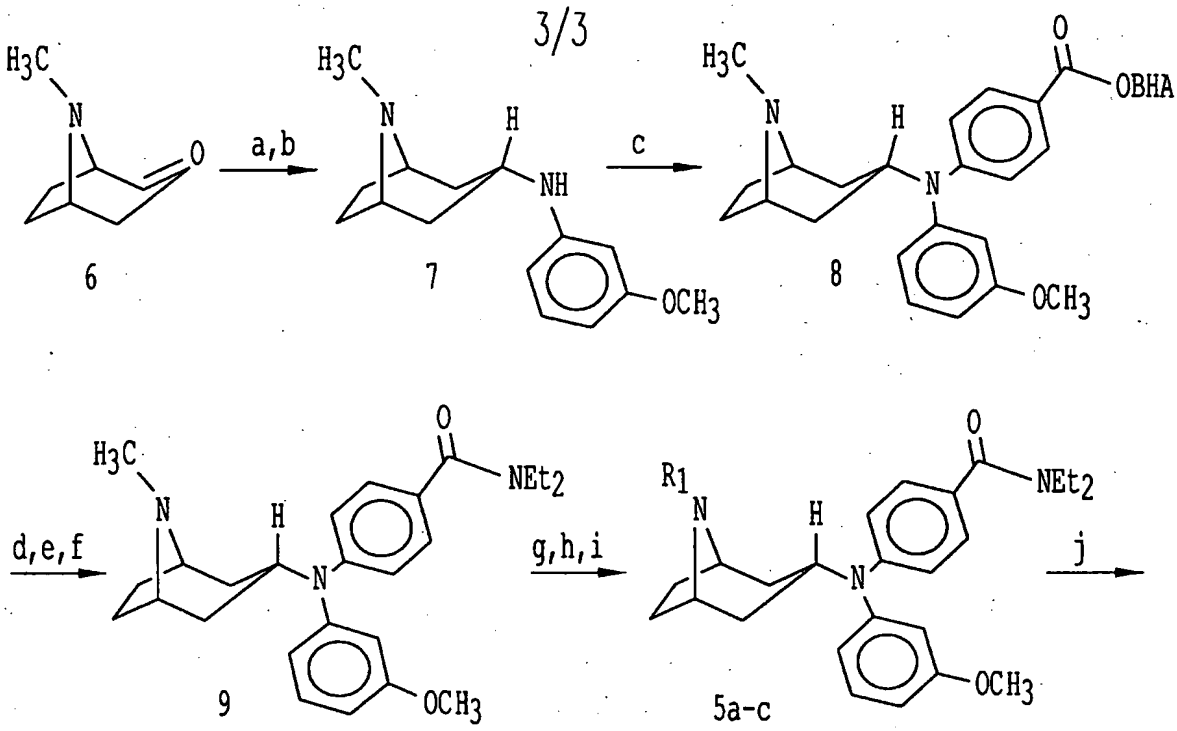


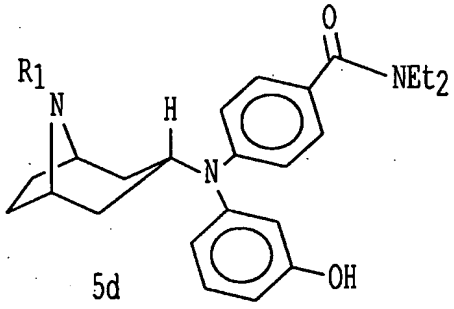
FIG. 2



5a: R_1= allyl

5b: R_1= cis-crotyl

5c: R_1= Prenyl



5d: R_1= allyl

(a) $Ti(Oi\text{-}Pr)_4$, 3-methoxyaniline

(b) $NaBH_4$, EtOH

(c) n-BuLi, THF, HMPA then 1-(2,6-di-tert-butyl-4-methoxy)-4-fluorobenzoate

(d) N-methylpyrrolidinone,$NaOCH_3$, toluene

(e) EtOH, H_2O

(f) Et_2NH, BOP, Et_3N

(g) PhOCOCl

(h) KOH, iPrOH, H_2O

(i) R_1-Br, EtOH, K_2CO_3

(j) BBr_3

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/08629

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) :A61K 31/46; C07D 451/04
US CL :546/124,125; 514/304
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/124,125; 514/304

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE-STRUCTURAL FORMULA SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	THOMAS et al. (+)-4-[(N-allyl-cis-3-methyl-4-piperidinyl)phenylamino]-N. N-diethyl benzamide displays selective binding for the delta opioid receptor. Bioorganic & Medicinal Chemistry Letters. October 1999, Vol. 9, No. 20, pages 3053-3056.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 07 MAY 2001	Date of mailing of the international search report 14 MAY 2001
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Dorothea Lawrence Fay BERNARD DENTZ Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998) *